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PhRMA

'99 MAY 11 P1:44

May 5, 1999

Dockets Management Branch(HFA-305)
Food and Drug Administration
5630 Fishers Lane, Rm 1061
Rockville, Maryland 20852

Re: Docket No. 98D-1168; Draft Guidance for Industry on ANDAs: Impurities in Drug Products; Notice of Availability and Request for Comments; Appearing in the Federal Register of Tuesday, January 5, 1999, (64FR516).

Dear Sir/Madam:

The Pharmaceutical Research and Manufacturers of America (PhRMA) represents the country's leading research-based pharmaceutical and biotechnology companies, which are devoted to inventing medicines that allow patients to lead longer, happier, healthier and more productive lives. Investing over $24 billion annually in discovering and developing new medicines, PhRMA companies are leading the way in the search for cures.

PhRMA members sponsor investigational new drug applications (INDs), new drug applications (NDAs), abbreviated new drug applications (ANDAs) and amendments and supplements thereto which may include documentation relating to the reporting, identification and qualification of impurities in drug products produced from chemically synthesized drug substances and would be affected by the subject draft guidance. On behalf of our members we offer the following general comments on the draft:

PhRMA agrees that ANDAs should include a scientific appraisal of degradation pathways, qualification of degradation products, and appropriate specification limits. We further agree with the draft guidance in referencing the ICH Q3B, Impurities in Drug Products Guidance, and the accompanying requirements for new drugs. However, there are four aspects of this draft that are objectionable, as summarized below.

1. Firstly, there is a provision for FDA to provide analytical methods through requests under the Freedom of Information Act (FOIA). Analytical methods and limits used in the process and/or for quality control purposes are developed by the innovator and submitted as part of the NDA. This information is proprietary information as it represents internal technical know how and trade secrets related to the drug substance and dosage form in question. FDA's NDA regulations state that "Manufacturing methods or processes, including quality control procedures," are not available for public disclosure unless they have been previously disclosed to the public or relate to a product or ingredient that has been abandoned, and they do not represent a trade secret or confidential commercial information.[1]

[1] 21 C.F.R. 314.430(g)(1) exempts disclosure of methods for manufacturing processes, including quality control procedures. We acknowledge; however, that 21 C.F.R. 314.430(e)(6) allows disclosure of analytical methods unless: (1) extraordinary circumstances, (2) method serves no regulatory or compliance purpose, and (3) the method falls within the exemption for trade secrets and confidential commercial information. Putting the two regulations together, it seems clear that analytical methods (like degradation assays) cannot be disclosed if they constitute manufacturing procedures, including quality control procedures.

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Therefore, analytical methods and limits, including degradation assay methods, should be held in confidence by the agency when submitted to an IND or NDA and should not be distributed through FOIA.

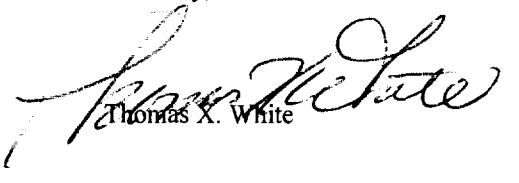
2. We also object to the provision in the draft for degradation product levels to exceed the reference drug by a factor of 2. These limits are qualified based on human and animal studies, and linked to the stability of the product. Doubling the limit that was accepted by the agency at the time of NDA approval is an advantage not available to the innovator, nor is it allowed by ICH Q3B and therefore should not be available to an ANDA sponsor. PhRMA is not aware of any established two-times rule for setting acceptance criteria for impurities and degradation products. Simple reliance on such a convention would result in generic ANDA products having impurity levels higher than the qualified level in the reference listed drug.

3. The draft guidance also allows qualification of new or higher level degradation products via structure-toxicology analysis (QSAR). This provision is not allowed for NDAs nor is it part of ICH Q3B. **QSAR should not be used in qualifying new or higher levels of degradation products in ANDAs.** Generally, QSAR alone is not recognized as adequate for CDER Pharmacology/Toxicology reviews. It is sometimes used as a preliminary prediction tool at the research stage and its application as a regulatory tool in qualifying an impurity cannot be justified. PhRMA strongly recommends that data from the scientific literature or actual laboratory data be required to support or confirm the QSAR analysis.

4. The basis for qualification of impurities for new products (i.e. NDAs) is genetic toxicology and whole animal toxicology testing according to ICH Q3B. The proposed ANDA guidance requires only QSAR analysis or in-vitro genetic toxicology, which is inadequate to assess the toxicology of new degradation products according to current FDA practice and ICH Q3B. Since FDA seems to be asserting in the draft guidance that additional (whole animal or in vivo) toxicology studies cannot be used for generic drug products, then, **in situations where new degradation products appear, we believe the product is substantially different from the innovator, and that an ANDA would be insufficient to assure safety and effectiveness for such a product.**

PhRMA appreciates the opportunity to provide comments on the subject draft guidance.

Sincerely,



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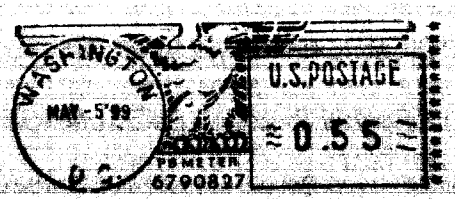

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